REMARKS

Applicant has carefully reviewed and considered the Office Action mailed on April 9, 2003, and the references cited therewith.

Claims 1-8 are pending, claim 1 is amended and new claims 51, 52 and 53 are added. As a result, claims 1-8 and 51-53 are now under examination in this application (claims 9-50 have been withdrawn from examination at this time). The subject matter of claim 1 has been amended to include the phrase "and wherein the stabilizing mutation removes an unfavorable electrostatic interaction in the Fn3." Support for subject matter relating to this phrase can be found throughout the specification, for example, at Page 35, Line 4 to Page 38, Line 30 and in Example XIX (see especially the title of this Example),

Support for new claim 51 is also present in the specification, for example, at Page 7, Lines 3-11, Page 35, Line 4 to Page 38, Line 30 and Example XIX. Support for new claim 52 is present in the specification, for example, at Page 6, Lines 27-29, Page 35, Line 4 to Page 38, Line 30 (e.g. Page 37, Lines 14-24) and Example XIX. Support for new claim 53 is present in the specification, for example, at Page 6, Lines 20-24, Page 37, Line 25 to Page 38, Line 1 and Example XIX. Applicant submits that claims 51-53 contain no new matter.

Restriction Requirement

The Examiner has maintained the requirement for restriction and has withdrawn claims 9-50 from prosecution. Applicant reserves the right to pursue examination of claims 9-50 in a continuation or divisional application.

Benefit Claim

The Examiner has indicated that reference to earlier filed applications should be made in order to obtain priority under 35 U.S.C. §119(e). Applicant has amended specification to claim benefit of U.S. Provisional Application Ser. No. 60/217474 filed July 11, 2000.

Specification

The Examiner has requested cooperation in correcting any errors of which Applicant may become aware. Applicant believes the specification is correct as filed. However, Applicant will amend the specification to correct any typographical errors that do become apparent.

Information Disclosure Statement

The Examiner has noted that references listed in the specification at pages 78-89 are not an Information Disclosure Statement. Applicant submits that these references were cited to provide technical procedures and background relating to the invention and Applicant has incorporated these references into the application to the extent that they can be. Such a listing of references is not a formal Information Disclosure Statement. Instead, Applicant has separately filed an Information Disclosure Statement with the application on July 11, 2001 as well as a Supplemental Information Disclosure Statement on April 11, 2002. Applicant thanks the Examiner for initialing the references cited in these Statements.

§102 Rejection of the Claims

Claims 1, 2, 6 and 8 were rejected under 35 USC § 102(b) as allegedly anticipated by WO 98/56915 to Koide or WO 00/34784 to Lipovsek. The Examiner has alleged that WO 98/56915 discloses a fibronectin polypeptide monobody comprising a plurality of fibronectin beta-strand domains that are linked to a plurality of loop region sequences, where one or more of the loop region sequences vary from the wild type fibronectin sequence by deletion, insertion or replacement. The Examiner further asserts that WO 00/34784 basically discloses the same fibronectin mutant as WO 98/56915.

Claim 1 is directed to a fibronectin type III (Fn3) molecule, wherein the Fn3 comprises a stabilizing mutation as compared to a wild-type Fn3 and wherein the stabilizing mutation removes an unfavorable electrostatic interaction in the Fn3. Claim 2 defines the stabilizing mutation as comprising at least one aspartic acid (Asp) residue that has been deleted or substituted with at least one other amino acid residue. Claim 6 defines the stabilizing mutation

as being at amino acid Glu 9 and as having been a deletion or substitution of Glu 9 with at least one other amino acid residue. Claim 8 is directed to a fibronectin type III molecule, wherein Asp 7, Asp 23, and Glu 9 have been deleted or substituted with at least one other amino acid residue.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ 2d 1913, 1920 (Fed. Cir. 1989). To constitute anticipation, the claimed subject matter must be identically disclosed in the prior art. *In re Arkley*, 172 U.S.P.Q. 524 at 526 (C.C.P.A. 1972). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the art. *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 101 (Fed. Cir. 1991). To overcome the defense of anticipation, "it is only necessary for the patentee to show some tangible difference between the invention and the prior art." *Del Mar Engineering Lab v. Physio-Tronics, Inc.*, 642 F.2d 1167, 1172, (9th Cir. 1981).

Applicant submits that neither WO 98/56915 (Koide) or WO 00/34784 (Lipovsek) discloses a fibronectin type III molecule that has a stabilizing mutation rendering the fibronectin type III molecule more stable than wild type fibronectin. Moreover, neither reference discloses a stabilizing mutation that removes an unfavorable electrostatic interaction in the Fn3. Procedures for making such a fibronectin type III molecule with such a stabilizing mutation are also lacking in WO 98/56915 (Koide) and WO 00/34784 (Lipovsek).

In particular, only mutant fibronectin molecules with reduced stability relative to wild type fibronectin are disclosed in WO 98/56915 (Koide) (*see, e.g.*, Figure 16 and Example XVII). The only disclosure on stability provided by WO 00/34784 (Lipovsek) relates to the stability of wild type human fibronectin (see page 13, lines 23-26). Neither reference discloses any useful description on how to remove electrostatic interactions. Hence, WO 98/56915 (Koide) and WO 00/34784 (Lipovsek) effectively provide no teaching on how to increase fibronectin stability.

Instead, WO 98/56915 (Koide) and WO 00/34784 (Lipovsek) are limited to a teaching of mutating fibronectin to generate molecules that bind a specific binding partner or target. For

example, WO 98/56915 (Koide) summarizes the invention in the first two sentences of the Summary of the Invention, as follows.

> The invention provides a fibronectin type III (Fn3) polypeptide monobody comprising a plurality of Fn3 β-strand domain sequences that are linked to a plurality of loop region sequences. One or more of the monobody loop region sequences of the Fn3 polypeptide vary by deletion, insertion or replacement of at least two amino acids from the corresponding amino acid sequence of wild type Fn3's β-strand domain sequences.

WO 98/56915 (Koide) at page 6, lines 12-19. WO 98/56915 (Koide) goes on to describe dividing the fibronectin gene into five parts so that loop regions can be mutated while the structure of Fn3 β-strand domain scaffold regions is preserved. *See*, page 18, line 4 to page 21, line 7. Such division would not be needed if Koide intended to mutate the Fn3 β-strand domain scaffold regions to increase Fn3 stability. Similarly, WO 00/34784 (Lipovsek) describes subjecting fibronectin-like molecules to directed evolution "to randomize one or more of the three fibronectin loops" (page 3, lines 4-8). See also WO 00/34784 (Lipovsek) at page 13, line 7-22; page 17, line 23 to page 19, line 2. Hence, WO 98/56915 (Koide) and WO 00/34784 (Lipovsek) do not disclose mutating fibronectin to achieve more stable fibronectin molecules.

The Examiner has noted that WO 98/56915 (Koide) discloses that seventeen FN3 domains are present in human fibronectin (see WO 98/56915 at page 17, lines 11-12). According to the Examiner such information on conserved residues is often important for the stability and folding of the protein. Consistent with the Examiner's comment, a high degree of conservation in a structural feature is generally recognized by one of skill in the art as indicating that the structural feature has an important structural or functional role in a molecule and the skilled artisan would normally choose to preserve the structural feature in order to preserve the overall structure or function of the molecule. However, the present application explains that several of the negatively charged amino acids in the wild type fibronectin that are highly conserved are also highly destabilizing (see specification at page 76, lines 6-20). Hence, the invention surprisingly advocates making stabilizing mutations in highly conserved amino acids in order to achieve higher stability. Applicant submits that any teaching by WO 98/56915

(Koide) on sequence conservation would guide the skilled artisan away from making the stabilizing mutations of the invention.

The examiner further states that Lipovsek basically discloses the same Fn3 mutant as Koide. In particular, the examiner states that page 17, lines 12-15 of Lipovsek discloses "substitutes of the Fn3 at other positions such as positions 1-9." Applicant respectfully disagrees with the examiner. The examiner appears to be mis-reading the abbreviations used in Lipovsek. The cited passage from Lipovsek discusses different modules of Fn3 (*i.e.*, whole molecules of Fn3), and not individual amino acid positions within an Fn3 molecule. No where in Lipovsek is it taught to modify specific amino acid positions within Fn3 in order to stabilize the molecule.

In conclusion, neither WO 98/56915 (Koide) or WO 00/34784 (Lipovsek) disclose a fibronectin type III molecule that has a stabilizing mutation. Hence, neither WO 98/56915 (Koide) nor WO 00/34784 (Lipovsek) anticipate the claimed subject matter, and Applicant respectfully requests withdrawal of this rejection of the claims under 35 U.S.C. § 102(b).

§103 Rejection of the Claims

Claims 1- 8 were rejected under 35 USC § 103(a) as allegedly unpatentable over WO 98/56915 to Koide or WO 00/34784 to Lipovsek in view of U.S. Patent 6,391,855 to Blaschuk. The Examiner asserts that WO 98/56915 (Koide) or WO 00/34784 (Lipovsek) discloses or suggests substituting amino acid residues Asp at position 7 and 9 or 23 with a library containing different amino acids.

The test for obviousness under § 103 must take into consideration the invention as a whole; that is, one must consider the particular problem solved by the combination of elements that define the invention. *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985). The Examiner must also recognize and consider not only the similarities but also the critical differences between the claimed invention and the prior art. *In re Bond*, 910 F.2d 831, 834, 15 U.S.P.Q.2d (BNA) 1566, 1568 (Fed. Cir. 1990), *reh'g denied*, 1990 U.S. App. LEXIS 19971 (Fed. Cir. 1990). Hindsight must also be avoided. *Id.* The Examiner cannot use the Appellant's structure as a "template" and simply select elements from the

references to reconstruct the claimed invention. *In re Gorman,* 933 F.2d 982, 987, 18 U.S.P.Q.2d (BNA) 1885, 1888 (Fed. Cir. 1991).

Applicant respectfully submits that the present claims are not obvious over the cited references. The Examiner has argued that WO 98/56915 (Koide) or WO 00/34784 (Lipovsek) suggests substituting Asp at positions 7, 9 or 23 with conservative substitutions and that U.S. Patent 6,391,855 to Blaschuk discloses what is a conservative substitution. In particular the Examiner cites to U.S. Patent 6,391,855 at col. 8, lines 53-66, which discloses that a "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. U.S. Patent 6,391,855 at col. 8, lines 53-66 further discloses that amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or amphipathic nature of the residues. According to the Examiner, U.S. Patent 6,391,855 at col. 8, lines 53-66 also teaches that negatively charged amino acids such as aspartic acid and glutamic acid can be substituted for each other.

Applicant submits that conservative substitutions in the fibronectin type III (Fn3) molecule would not remove an unfavorable electrostatic interaction in the Fn3 as required by claim 1. As explained in the specification at page 37, lines 12-24, the spatial proximity of negatively charged amino acid residues contributes to unfavorable electrostatic interactions in Fn3. However, substitution of Glu for Asp or *vice versa* would not eliminate the negative charge at a given position and would therefore not remove an unfavorable electrostatic interaction in Fn3. Hence, the conservative substitutions taught by U.S. Patent 6,391,855 would not guide one of skill in the art to the present invention.

The Examiner further asserts that the combination or references U.S. Patent 6,391,855 at col. 8, lines 53-66 teaches that any charged amino acid can be substituted for another charged amino acid, suggesting that U.S. Patent 6,391,855 teaches that substitution of a positively charged amino acid like Lys for a negatively charged amino like Glu would be a conservative substitution. However, Applicant fails to find such a teaching in U.S. Patent 6,391,855 or in any

of the other references cited by the Examiner. The text from U.S. Patent 6,391,855 that is relied upon by the Examiner is as follows:

> A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

A careful reading of U.S. Patent 6,391,855 to Blaschuk indicates that this reference teaches that amino acids with **similar** polarity or charge can be substituted for each other. Negatively charged amino acids like Asp and Glu are not similar to in polarity or charge to positively charged amino acids like Lys or Arg. Hence, U.S. Patent 6,391,855 to Blaschuk does not disclose or suggest substitution of negatively charged amino acids with positively charged amino acids. In fact, Blaschuk instead teaches away from the present invention because Blaschuk teaches substituting amino acids with similar polarity or charge rather than substituting amino acids with different polarity or charge.

Applicant further submits that WO 98/56915 (Koide) and WO 00/34784 (Lipovsek) are limited to a teaching of mutating fibronectin to generate molecules that bind a specific binding partner or target, not to generate molecules with greater stability. As described in the present specification at page 35, and as illustrated by WO 98/56915 (Koide) in Example XVII (and Figure 16), such mutations are almost invariably destabilizing. The present specification at page 35, lines 17-27 states the following:

> The inventor found that, although Fn3 is an excellent scaffold, Fn3 variants that contain large number of mutations are destablized against chemical denaturation, compared to the wild-type Fn3 protein (Koide *et*

> *al.*, 1998). Thus, as the number of mutated positions are mutated in order to engineer a new binding function, the stability of such Fn3 variants further decreases, ultimately leading to marginally stable proteins. Because artificial binding proteins must maintain their three-dimensional structure to be functional, stability limits the number of mutations that can be introduced in the scaffold.

Such observations are further corroborated by results provided in WO 98/56915 (Koide). In particular, only mutant fibronectin molecules with reduced stability relative to wild type fibronectin are disclosed in WO 98/56915 (Koide) (*see, e.g.*, Figure 16 and Example XVII). Hence, the mutations described by WO 98/56915 (Koide) and WO 00/34784 (Lipovsek) achieve lower rather than higher stability.

Accordingly, the combination of WO 98/56915 (Koide), WO 00/34784 (Lipovsek) and U.S. Patent 6,391,855 (Blaschuk) does not disclose or teach the subject matter of claims 1-8, 51-53. Applicant respectfully requests withdrawal of this rejection under 35 U.S.C. § 103(a).

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (516-795-6820) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 9 day of July, 2003.

CANDIS BRENDWIG
Name

Signature